Claims 1-8, 10, and 13-24 were rejected under 35 U.S.C. § 112, first paragraph, for reasons set forth in the Office Action mailed February 22, 1999 (Paper No. 29). Applicants note that Paper No. 29 appears to set forth no additional reasons for the rejection beyond those presented in Paper No. 32.

37 C.F.R. § 1.113(b) states:

> In making such final rejection, the examiner shall repeat or state all grounds of rejection then considered applicable to the claims in the application, clearly stating the reasons in support thereof.

Furthermore, M.P.E.P. § 706.07 states:

> In making the final rejection, all outstanding grounds of rejection of record should be carefully reviewed, and any such grounds relied on in the final rejection should be reiterated. They must also be clearly developed to such an extent that applicant may readily judge the advisability of an appeal unless a single previous Office action contains a complete statement supporting the rejection. However, where a single previous Office action contains a complete statement of a ground of rejection, the final rejection may refer to such a statement and also should include a rebuttal of any arguments raised in the applicant's response.

If, in making this rejection, the Examiner is relying on grounds not stated in Paper No. 29 or Paper No. 32, applicants respectfully request withdrawal of the finality of the Office Action, and issuance of a new Office Action clearly stating these grounds, so that applicants can more fully respond to the rejections and may more readily judge the advisability of an Appeal.

Applicants assume that the statutory basis for this rejection is for allegedly failing to adequately teach one skilled in the art how to make and/or use the claimed invention. The Examiner contends that it is apparent that numerous modified *Shigella* are required to practice

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D.C. 20005
202-408-4000

the claimed invention. The Examiner contends that applicants' arguments in support of enablement are not fully persuasive in view of Baudry et al.'s disclosure that the invasive ability of *S. flexerni* is a very complex phenomenon, which involves many genes, and that it is unclear whether all these gene products are directly involved in the interaction with the cells. The Examiner further contends that the skilled artisan would be forced into undue experimentation to determine which genes or combination of genes, and which modifications can be made to inactivate genes. The Examiner contends that Prentki et al.'s disclosure of difficulties with transposon-mediated mutagenesis is relevant to the enablement of the claimed invention because transposon-mediated mutagenesis is encompassed within the scope of the claimed invention if combined with another method of mutation. Applicants traverse the rejection.

Applicants method of mutagenesis is **not** transposon mutagenesis. To more clearly point this out, applicants have amended claims 1 and 13 to recite that the *Shigella* is transformed "other than by inactivation by means of a transposon inserted into the genes". Although the mutated gene might additionally contain a transposon, applicants claimed invention only requires that the gene has been inactivated by other means. Since the gene is inactivated by other means, the difficulties of transposon-mediated mutagenesis disclosed in Prentki et al. would be irrelevant to the enablement of the claimed invention.

As applicants previously submitted in applicants' April 17, 1998, and January 20, 1999, Amendments, the mutagenesis technique of Prentki et al., which is taught by the specification, does not require knowledge of the nucleotide sequence of the target genes or knowledge of the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D.C. 20005
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regions of genes responsible for biological activity. The number of nucleotides deleted or inserted is not critical to claimed invention. The prior art discloses a wealth of information concerning the genes involved in the spread and invasion of *Shigella* and the requisite screening procedures for screening for mutations in *Shigella* genes that affect the invasion of cells, spread within infected cells, and toxin production. Genetic targets and techniques for such screening were known to the skilled artisan and, in combination with the guidance of the specification, enable the skilled artisan to make and use the claimed invention without undue experimentation.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Furthermore, the Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1561, 27 U.S.P.Q. 2d 1510, 1515 (Fed. Cir. 1993).

As detailed above and in applicants' April 17, 1998, and January 20, 1999, Amendments, the skilled artisan expects success in practicing the claimed invention, and the claimed invention is predictable and requires no undue experimentation. In the absence of any evidence that undue experimentation would be necessary to practice the claimed invention, applicants respectfully request withdrawal of the rejection.

Claims 13 and 14 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
202-408-4000

time the application was filed. The Examiner contends that the specification does not provide support for claiming an entire genus of the species *Shigella* based on the preferred embodiments. Applicants traverse the rejection.

M.P.E.P. § 2163.04 states:

> The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. 541 F.2d at 265, 191 USPQ at 98. See also Ex parte Sorenson, 3 USPQ2d 1462, 1463 (Bd. Pat. App. & Inter. 1987) . . . Any time an examiner bases a rejection of a claim or the denial of the effect of a filing date of a previously filed application on the lack of a written description, the examiner should: (A) identify the claim limitation not described; and (B) provide reasons why persons skilled in the art at the time the application was filed would not have recognized the description of this limitation in the disclosure of the application as filed. A typical reason points out the differences between what is disclosed and what is claimed. A simple statement that "There does not appear to be a written description of the claim limitation `_____' in the application as filed." may be sufficient where the support is not apparent and the applicant has not pointed out where the limitation is supported. . . . **If applicant amends the claims and points out where and/or how the originally filed disclosure supports the amendment(s), and the examiner finds that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of the filing of the application, the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.** Accordingly, the examiner should identify what portion(s) of the amendment lack support in the originally filed disclosure, and should fully explain the basis for the examiner's finding. The examiner also should comment on the substance of applicant's remarks.

Applicants have pointed out where and how the originally filed disclosure supports the claims. See January 20, 1999, Amendment at 10-12. Applicants submit that the Examiner has

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
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not met his burden since the Examiner has provided no reasons why the skilled artisan would not recognize in the disclosure a description of the invention defined by the claims.

Furthermore, applicants cloned the shiga toxin operon, generated mutants by *in vitro* mutagenesis, and generated Tox- *Shigella* by allelic exchange. (Specification at 9-23). Specific embodiments SC501, SC504, SC504, and SC506 were described. (Id. at 9-23). The specification teaches that the described embodiments are merely preferred embodiments, and that various modifications can be made. (Id at 23).

The written description requirement may be satisfied if the broader concept would naturally occur to one skilled in the art upon reading the specification. In re Wright, 866 F.2d 422, 424, 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1989). Here, the broader concept that Tox- *Shigella* other than SC501, SC504, SC504, and SC506 could be generated by minor modification of applicants' methods would naturally occur to the skilled artisan. Accordingly, applicants respectfully submit that the written description requirement of 35 U.S.C. § 112, first paragraph, has been fulfilled, and respectfully request withdrawal of the rejection.

Applicants respectfully submit that this application is in condition for allowance and request the issuance of a Notice of Allowance. If the Examiner should disagree, he is invited to contact the undersigned to discuss any remaining issues.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D.C. 20005
202-408-4000

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: _____
Kenneth J. Meyers
Reg. No. 25,146

Dated: September 9, 1999

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D.C. 20005
202-408-4000